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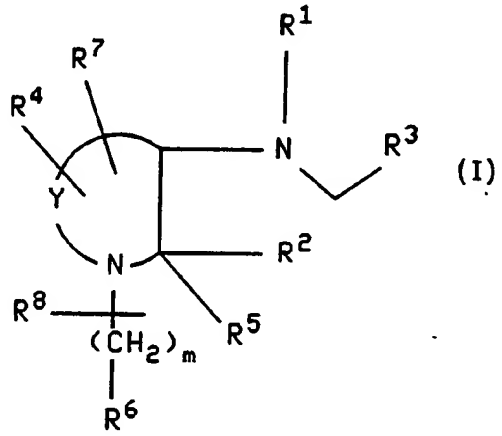

(I)

(57) Abstract

The present invention relates to novel 3-amino-piperidine derivatives and related nitrogen containing heterocyclic compounds, and specifically, to compounds of formula (I) wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, Y and m are as defined below. These novel compounds are useful in the treatment of inflammatory and central nervous system disorders, as well as other disorders. The invention also relates to novel intermediates used in the synthesis of compounds of formula (I).

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3-AMINOPIPERIDINE DERIVATIVES AND RELATED NITROGEN CONTAINING HETEROCYCLES

Background of the Invention

The present invention relates to novel 3-aminopiperidine derivatives and related compounds, pharmaceutical compositions comprising such compounds and the use of such compounds in the treatment and prevention of inflammatory and central nervous system disorders, as well as several other disorders. The pharmaceutically active compounds of this invention are substance P antagonists. This invention also relates to novel intermediates used in the synthesis of such substance P antagonists.

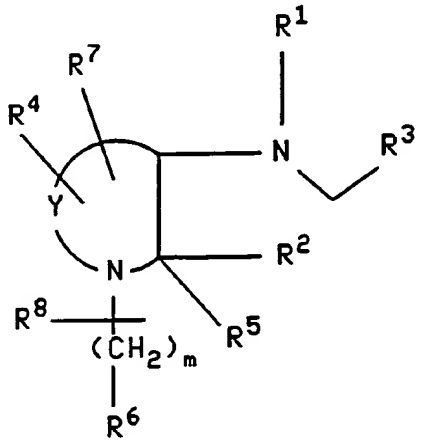
Substance P is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the latter being named because of their prompt stimulatory action on smooth muscle tissue. More specifically, substance P is a pharmacologically active neuropeptide that is produced in mammals (having originally been isolated from gut) and possesses a characteristic amino acid sequence that is illustrated by D. F. Veber et al. in U.S. Patent No. 4,680,283. The wide involvement of substance P and other tachykinins in the pathophysiology of numerous diseases has been amply demonstrated in the art. For instance, substance P has recently been shown to be involved in the transmission of pain or migraine (see B.E.B. Sandberg et al., Journal of Medicinal Chemistry, 25, 1009 (1982)), as well as in central nervous system disorders such as anxiety and schizophrenia, in respiratory and inflammatory diseases such as asthma and rheumatoid arthritis, respectively, in rheumatic diseases such as fibrositis, and in gastrointestinal disorders and diseases of the GI tract such as ulcerative colitis and Crohn's disease, etc. (see D. Regoli in "Trends in Cluster Headache," edited by F. Sicuteri et al., Elsevier Scientific Publishers, Amsterdam, pp. 85-95 (1987)).

In the recent past, some attempts have been made to provide antagonists for substance P and other tachykinin

peptides in order to more effectively treat the various disorders and diseases listed above. The few such antagonists thus far described are generally peptide-like in nature and are therefore too labile from a metabolic point of view to serve as practical therapeutic agents in the treatment of disease. The non-peptidic antagonists of the present invention, on the other hand, do not possess this drawback, being far more stable from a metabolic point of view than the agents referred to above.

Summary of the Invention

The present invention relates to compounds of the formula



I

wherein Y is $(CH_2)_n$ wherein n is an integer from 1 to 6, and wherein any one of the carbon-carbon single bonds in said $(CH_2)_n$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_n$ may optionally be substituted with R^4, and wherein any one of the carbon atoms of said $(CH_2)_n$ may optionally be substituted with R^7;

m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of $(CH_2)_m$ may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^8;

R^1 is hydrogen or (C_1-C_8) alkyl optionally substituted with hydroxy, alkoxy or fluoro;

R^2 is a radical selected from hydrogen, (C_1-C_6) straight or branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, amino, (C_1-C_6)-alkylamino, (C_1-C_6)alkyl-O-$\overset{O}{\overset{\|}{C}}$-, (C_1-C_6)alkyl-O-$\overset{O}{\overset{\|}{C}}$-$(C_1-C_6)$alkyl, (C_1-C_6)alkyl-$\overset{O}{\overset{\|}{C}}$-O-, (C_1-C_6)alkyl-$\overset{O}{\overset{\|}{C}}$-$(C_1-C_6)$alkyl-O-, (C_1-C_6)alkyl-$\overset{O}{\overset{\|}{C}}$-, (C_1-C_6)alkyl-$\overset{O}{\overset{\|}{C}}$-$(C_1-C_6)$alkyl-, di-$(C_1-C_6)$alkylamino, -$\overset{O}{\overset{\|}{C}}$NH-$(C_1-C_6)$alkyl, (C_1-C_6)-alkyl-$\overset{O}{\overset{\|}{C}}$-NH-$(C_1-C_6)$alkyl, -$\overset{O}{\overset{\|}{C}}$NHCH and -$\overset{O}{\overset{\|}{C}}$NHC-$(C_1-C_6)$ alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

R^5 is hydrogen, phenyl or (C_1-C_6)alkyl;

or R^2 and R^5, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by oxygen, nitrogen or sulfur;

R^3 is aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; and cycloalkyl having 3 to 7

carbon atoms wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said (C_3-C_7) cycloalkyl may optionally be substituted with one or two substituents, each of said substituents being independently selected from halo, nitro, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, phenyl, amino, (C_1-C_6) alkylamino, $-\overset{O}{\overset{\|}{C}}-NH-(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-\overset{O}{\overset{\|}{C}}-$ $NH-(C_1-C_6)alkyl$, $-NH\overset{O}{\overset{\|}{C}}H$ and $-NH\overset{O}{\overset{\|}{C}}-(C_1-C_6)alkyl$; and

R^4 and R^7 are each independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), nitrile, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, $(C_1-C_6)alkyl-O-\overset{O}{\overset{\|}{C}}-$, $(C_1-C_6)alkyl-O-\overset{O}{\overset{\|}{C}}-(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-\overset{O}{\overset{\|}{C}}-O-$, $(C_1-C_6)alkyl-\overset{O}{\overset{\|}{C}}-(C_1-C_6)alkyl-O-$, hydroxy-($C_1$-$C_6$)alkyl, ($C_1$-$C_6$)alkoxy($C_1$-$C_6$)alkyl $(C_1-C_6)alkyl-\overset{O}{\overset{\|}{C}}-$, $(C_1-C_6)alkyl-\overset{O}{\overset{\|}{C}}-(C_1-C_6)alkyl-$, and the radicals set forth in the definition of R^2,

R^6 is $NH\overset{O}{\overset{\|}{C}}R^9$, $NHCH_2R^9$, SO_2R^9 or one of the radicals set forth in any of the definitions of R^2, R^4 and R^7;

R^8 is oximino (=NOH) or one of the radicals set forth in any of the definitions of R^2, R^4 and R^7;

R^9 is (C_1-C_6)alkyl, hydrogen, phenyl or phenyl (C_1-C_6)alkyl;

with the proviso that (a) when m is 0, R^8 is absent, (b) neither R^4, R^6, R^7 nor R^8 can form, together with the carbon to which it is attached, a ring with R^5, (c) when R^4 and R^7 are attached to the same carbon atom, then either each of

R^4 and R^7 is independently selected from hydrogen, fluoro and (C_1-C_6) alkyl, or R^4 and R^7, together with the carbon to which they are attached, form a (C_3-C_6) saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are attached, (d) when n is 2 and either R^4 or R^7 is 5-hydroxy(C_1-C_6)alkyl or 5-(C_1-C_6)alkoxy-(C_1-C_6)alkyl, then the other of R^4 and R^7 is hydrogen, (e) when n is 2, neither R^4 nor R^7 is 4-hydroxy(C_1-C_6)alkyl or 4-(C_1-C_6)alkoxy-(C_1-C_6)alkyl, and (f) in all compounds of the formula I, either R^3 is aryl substituted with at least one phenyl group, or one or both of R^4 and R^7 is hydroxy-(C_1-C_6)alkyl or (C_1-C_6)alkoxy(C_1-C_6)alkyl.

By proviso (f) above is meant that in all compounds of the formula I, one or both of the following conditions A and B must occur. Condition A occurs when R^3 is aryl substituted with at least one phenyl group and condition B occurs when one or both of R^4 and R^7 is hydroxy-(C_1-C_6)alkyl or (C_1-C_6)alkoxy(C_1-C_6)alkyl.

The present invention also relates to the following compounds, which are hereinafter referred to as "the Group II compounds":

(2S,3S)-3-(4,5-difluoro-2-methoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(2-cyclopentyloxy-5-methoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(5-sec-butyl-2-methoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(5-tert-butyl-2-methoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(2-cyclopentyloxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(2-acetamidobenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(5-ethyl-2-methoxybenzyl)amino-2-phenylpiperidine hydrochloride;

(2S,3S)-3-(4-amino-5-chloro-2-methoxybenzyl)amino-2-phenylpiperidine hydrochloride;

(2S,3S)-2-phenyl-3-(quinolin-8-yl)methylpiperidine hydrochloride;

(2S,3S)-3-(5-heptyloxy-2-methoxybenzyl)amino-2-phenylpiperidine hydrochloride;

(2S,3S)-3-(2-heptyloxy-5-methoxybenzyl)amino-2-phenylpiperidine hydrochloride;

(2S,3S)-3-(5-heptyl-2-methoxybenzyl)amino-2-phenylpiperidine hydrochloride;

(2S,3S)-3-(2-ethylaminobenzyl)amino-2-phenylpiperidine hydrochloride;

(2S,3S)-1-(5,6-difluorohex-1-yl)-3-(2-methoxybenzyl)-amino-2-phenylpiperidine hydrochloride;

(2S,3S)-3-(2-methoxy-5-n-propylbenzyl)amino-2-phenylpiperidine hydrochloride;

(2S,3S)-3-(4,5-dimethyl-2-methoxybenzyl)amino-2-phenylpiperidine hydrochloride;

(2S,3S)-3-(5-t-butyl-2-hydroxybenzyl)amino-2-phenylpiperidine hydrochloride;

(2S,3S)-3-(5-carbomethoxy-2-methoxybenzyl)amino-2-phenylpiperidine hydrochloride;

(2S,3S)-3-(5-n-butyl-2-methoxybenzyl)amino-2-phenylpiperidine hydrochloride;

(2S,3S)-3-(5-isopropyl-2-methoxybenzyl)amino-2-phenylpiperidine hydrochloride;

(2S,3S)-1-(4-t-butyramidobut-1-yl)-3-(2-methoxybenzyl)-amino-2-phenylpiperidine hydrochloride;

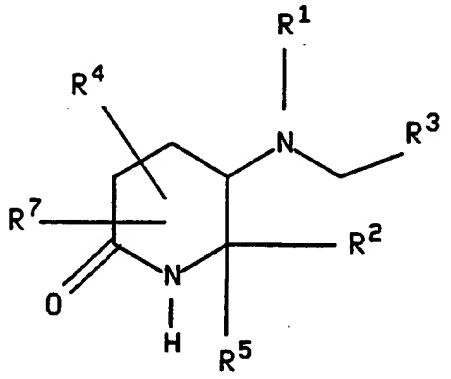
(2S,3S)-(3-benzamidoprop-1-yl)-3-(2-methoxybenzyl)-amino-2-phenylpiperidine hydrochloride; and

cis-3-(5-cyclopentyl-2-methoxybenzyl)amino-2-phenylpiperidine hydrochloride.

The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I and the Group II compounds. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing

pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3- naphthoate)]salts.

The present invention also relates to compounds of the formula



VII

wherein R^1, R^2, R^3, R^4, R^5 and R^7 are as defined for compounds of the formula I. The compounds of the formula VII are novel intermediates used in the synthesis of compounds of the formula I and the Group II compounds.

The present invention also relates to the compound 3-amino-2-phenylpiperidine.

The term "halo", as used herein, unless otherwise indicated, includes chloro, fluoro, bromo and iodo.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "one or more substituents," as used herein, includes from one to the maximum number of substituents possible based on the number of available bonding sites.

The present invention also relates to a pharmaceutical composition for treating or preventing a condition selected

from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypertension, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis in a mammal, including a human, comprising an amount of a compound of the formula I or a Group II compound, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such condition, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypertension, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to immune enhancement or

suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I or a Group II compound, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such condition.

The present invention also relates to a pharmaceutical composition for antagonizing the effects of substance P in a mammal, including a human, comprising a substance P antagonizing amount of a compound of the formula I or a Group II compound, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of antagonizing the effects of substance P in a mammal, including a human, comprising administering to said mammal a substance P antagonizing amount of a compound of the formula I or a Group II compound, or a pharmaceutically acceptable salt thereof.

The present invention also relates to a pharmaceutical composition for treating or preventing a disorder in a mammal, including a human, resulting from an excess of substance P, comprising a substance P antagonizing amount of a compound of the formula I or a Group II compound, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a disorder in a mammal, including a human, resulting from an excess of substance P, comprising administering to said mammal a substance P antagonizing amount of a compound of the formula I or a Group II compound, or a pharmaceutically acceptable salt thereof.

The present invention also relates to a pharmaceutical composition for treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, allergies such as eczema and

rhinitis, chronic obstructive airways disease, hypertension, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis in a mammal, including a human, comprising an amount of a compound of the formula I or a Group II compound, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypertension, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I or a Group II compound, or a

pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site.

The present invention also relates to a pharmaceutical composition for treating or preventing a disorder in a mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound of the formula I or a Group II compound, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a disorder in mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising administering to said mammal an amount of a compound of the formula I or a Group II compound, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site.

The present invention also relates to a pharmaceutical composition for treating or preventing a disorder in a mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound of the formula I or a Group II compound, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a disorder in mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising administering to said mammal an amount of a compound of the formula I or a Group II compound, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder.

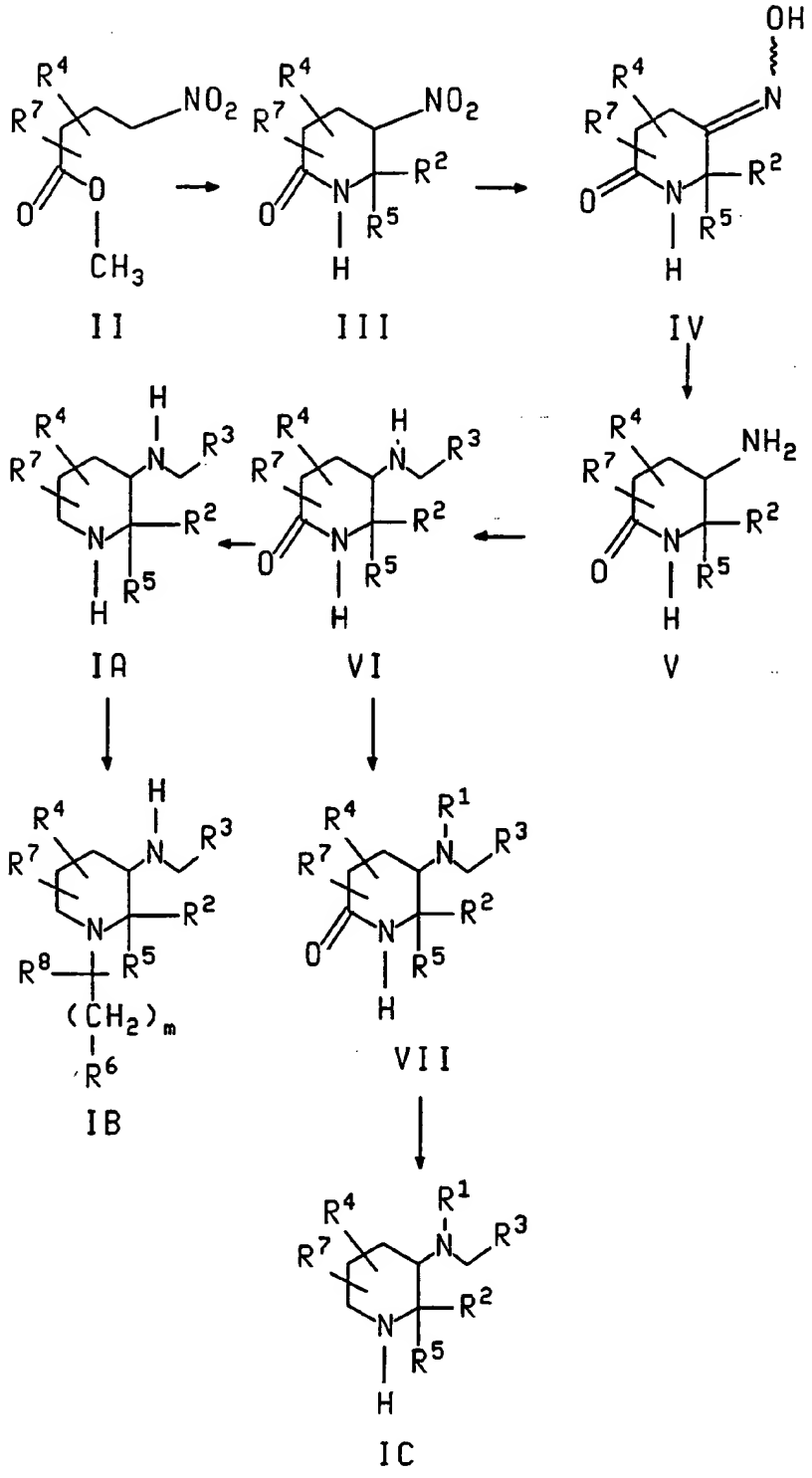
The compounds of the formula I have chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers and all stereoisomers of compounds of the formula I and the Group II compounds, and mixtures thereof.

Formulae I and VII above include compounds identical to those depicted but for the fact that one or more hydrogen or carbon atoms are replaced by radioactive isotopes thereof. Such radiolabelled compounds are useful as research and diagnostic tools in metabolism pharmokinetic studies and in binding assays. Specific applications in research include radioligand binding assays, autoradiography studies and in vivo binding studies, while specific applications in the diagnostic area include studies of the substance P receptor in the human brain in in vivo binding in the relevant tissues for inflammation, e.g. immune-type cells or cells that are directly involved in inflammatory bowel disorders and the like. Included among the radiolabelled forms of compounds of the formulae I and VII are the tritium and C^{14} isotopes thereof.

Detailed Description of the Invention

The compounds of the formula I and the Group II compounds may be prepared as described in the following reaction schemes and discussion. Each of the formulae designated IA, IB, IC, and ID represents a different group of compounds having the general formula I. Unless otherwise indicated, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, Y, n and m in the reaction schemes and discussion that follow are defined as above.

SCHEME 1



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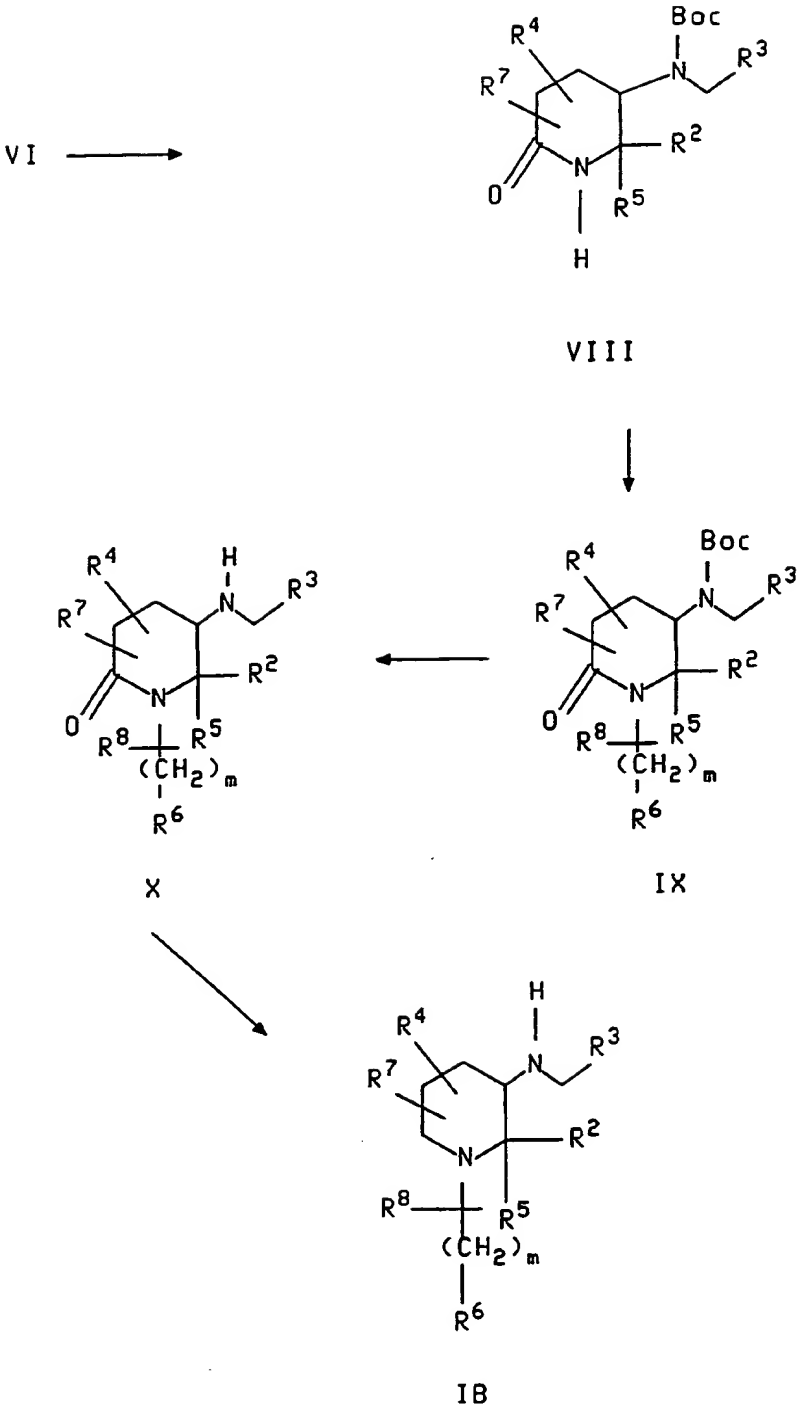

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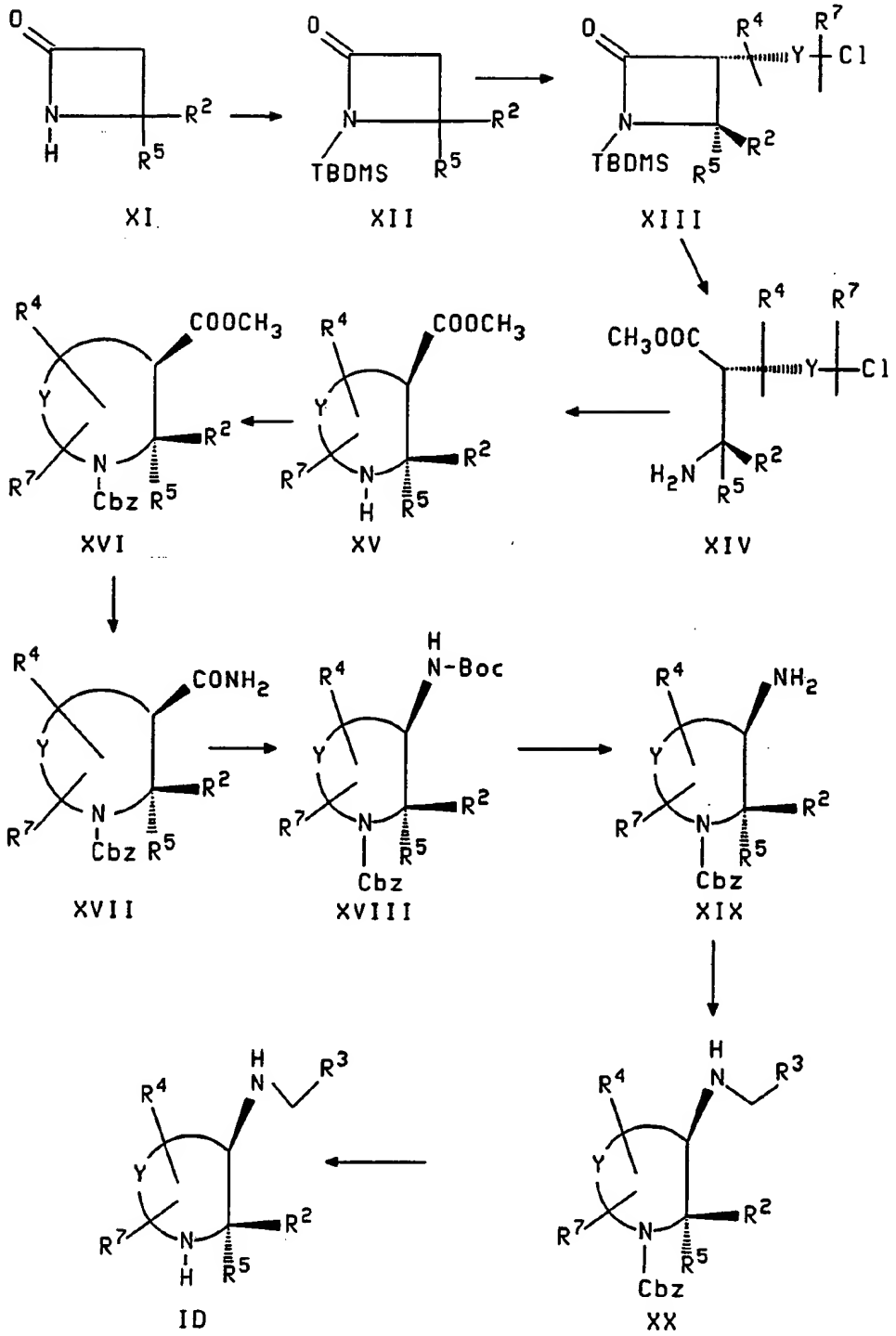

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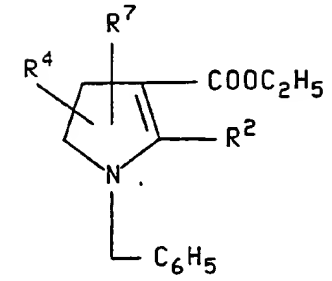

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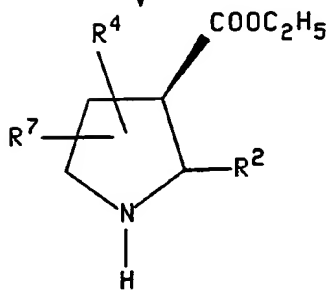
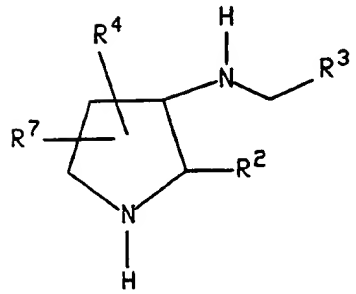


SCHEME 3



ID

Scheme 1 illustrates the preparation of compounds of the formulae IA, IB and IC. Formula IA represents compounds of the formula I wherein each of R^1 and R^6 is hydrogen, m is 0 and n is 3, with the proviso that R^2 is not benzhydryl and neither R^4 nor R^7 is attached to the "6" position of the piperidine ring. Formula IB represents compounds of the formula I wherein R^1 is hydrogen and n is 3, with the proviso that R^2 is not benzhydryl and neither R^4 nor R^7 is attached to the "6" position of the piperidine ring. Formula IC represents compounds of the formula I wherein R^6 is hydrogen, m is 0 and n is 3, with the proviso that R^2 is not benzhydryl and neither R^4 nor R^7 is attached to the "6" position of the piperidine ring.

Referring to scheme 1, a compound of the formula II

is reacted with a compound of the formula $R^5-\overset{O}{\overset{\|}{C}}-R^2$ in the presence of ammonium acetate, in a polar solvent such as ethanol, acetic acid or dimethyl sulfoxide. Ethanol is the preferred solvent. Temperatures from about room temperature to about 150°C are suitable, with the reflux temperature of the solvent being preferred. This reaction yields, by intramolecular condensation, a compound of the formula III (Von M. Muhlstadt and B. Schulze, J. Prak. Chem, 317, 919 (1975)).

The condensation product of formula III is then converted, via a Nef reaction, to an oxime of the formula IV. This reaction may be carried out using reagents such as aqueous Ti(III) chloride, potassium permanganate, pyridine/hexamethylphosphoramide complex of molybdenum pentoxide, tributylphosphinediphenyl disulphide or ozone in the presence of a base. Suitable temperatures range from about -100°C to about 0°C. Preferably, the reaction is performed by bubbling ozone through the reaction mixture in the presence of potassium t-butoxide at about -78°C, and then quenching the reaction mixture with hydroxylamine hydrochloride at ambient temperature.

The oxime of formula IV is then reduced to yield both the cis and trans isomers of a compound of the formula V. Suitable reducing agents include Raney nickel/hydrogen, 10% palladium on charcoal/hydrogen, and aluminum amalgam. Preferably, the reduction is carried out using Raney nickel in ethanol under a hydrogen gas pressure of about 3 atm and at a temperature of about 25°C. Temperatures from about 10°C to about 60°C and pressures from about 1 to about 10 atmospheres are also suitable.

Reductive amination of the mixture of cis and trans isomers of the compound of the formula V from the above step with sodium cyanoborohydride or sodium triacetoxyborohydride and a compound of the formula R^3CHO yields a mixture of the cis and trans isomers of a compound of the formula VI. This reaction is typically carried out in a polar solvent such as acetic acid or a lower alkanol, at a temperature from about 0°C to about 50°C. Methanol is the preferred solvent and about 25°C is the preferred temperature. It is also preferable that the pH of the reaction mixture be about 4 to about 5. The cis and trans isomers of the compound of the formula VI so formed can be easily separated by using silica-gel flash chromatography, eluting with 3% methanol in methylene chloride.

Reduction of either the cis or trans isomer of the compound of formula VI, or a mixture thereof, yields a compound of the formula IA having the same stereochemistry. Suitable reducing agents include borane dimethylsulfide in tetrahydrofuran ("THF"), lithium aluminum hydride, borane in THF and sodium borohydride-titanium (IV) chloride. Best results are obtained by using borane dimethylsulfide in THF. The reaction may be carried out at temperatures from about room temperature to about 150°C, and is preferably carried out at the reflux temperature of the solvent.

The compound of formula IA so formed may be converted to a compound of the formula IB having the same stereochemistry, as illustrated in scheme 1, by reacting it with a compound of the formula $R^6-(CH_2)_m-X$, wherein X is

halo, wherein one of the carbon-carbon single bonds of said $(CH_2)_m$ may optionally be replaced by a carbon-carbon double bond, and wherein one of the carbons of said $(CH_2)_m$ may optionally be substituted with R^8. This reaction is typically carried out in the presence of a base such as triethylamine or potassium t-butoxide, in a polar solvent such as methylene chloride or dichloroethane, and at a temperature from about room temperature to about 150°C. Preferably, the reaction is carried out at the reflux temperature in methylene chloride in the presence of triethylamine.

Compounds of the formula IC may be prepared as illustrated in scheme 1 and described below. A compound of the formula VI is reacted with a compound of the formula R^1X, wherein X is halo, to yield a compound of the formula VII having the same stereochemistry (e.g. cis, trans or a mixture thereof). This reaction is typically carried out in the presence of a base such as triethylamine or potassium t-butoxide in a polar solvent such as methylene chloride or dichloroethane, at a temperature from about room temperature to about 150°C. Preferably, the reaction is carried out at about the reflux temperature in methylene choride in the presence of triethylamine.

Reduction of the compound of formula VII so formed yields a compound of the formula IC having the same stereochemistry. Examples of suitable reducing agents are lithium aluminum-hydride, borane dimethylsulfide in THF, borane in THF and sodium borohydride-titanium (IV) chloride. Best results are obtained using borane dimethylsulfide in THF. The reaction may be carried out at temperatures from about room temperature to about 150°C, and is preferably carried out at the reflux temperature of the solvent.

Scheme 2 illustrates an alternate method of preparing compounds of the formula IB. The starting material for this method is a compound of the formula VI, which is illustrated in scheme 1. In the first step of this method,

the basic nitrogen of the starting material is protected with a group such as t-butoxycarbonyl (Boc), trifluoroacetyl, carbobenzyloxy or carboethoxy, by reacting it, respectively, with di-t-butyl dicarbonate, trifluoroacetic anhydride, benzyl chloroformate or ethylchloroformate. The preferred protecting group, t-butoxycarbonyl, is illustrated in scheme 2. The reaction of the starting material with di-t-butyl dicarbonate is typically carried out in a polar solvent such as THF, dichloromethane or chloroform, at a temperature from about 0°C to about 100°C. The preferred solvent is dichloromethane and the preferred temperature is room temperature. The reaction is generally carried out for about 0.5 to 72 hours. This reaction yields a compound of the formula VIII having the same stereo- chemistry as the starting material.

The compound of formula VIII so formed is then reacted with a compound of the formula $X-(CH_2)_m-R^6$ wherein X is halo, or $CH_3SO_2O-(CH_2)_m-R^6$, to form a compound of the formula IX having the same stereochemistry. In each of $X-(CH_2)_m-R^6$ and $CH_3SO_2O-(CH_2)_m-R^6$, one of the carbons of said $(CH_2)_m$ may optionally be substituted with R^8 and one of the carbon-carbon single bonds of said $(CH_2)_m$ may optionally be replaced with a carbon-carbon double bond or a carbon-carbon triple bond. This reaction is generally carried out in the presence of a base such as potassium hydroxide, potassium t-butoxide, lithium diisopropylamine or sodium methoxide, in a polar solvent such as t-butanol or DMF, for about 0.5 to about 24 hours. The preferred base is potassium t-butoxide and the preferred solvent is t-butanol. Reaction temperatures will generally range from about -25°C to about 150°C. The preferred temperature is generally the reflux temperature of the solvent.

The protecting group is then removed from the compound of formula IX by reacting it with an acid such as hydrochloric acid, trifluoroacetic acid or perchloric acid, to yield a compound of the formula X having the same

stereochemistry. Appropriate solvents for this reaction include polar solvents such as methylene chloride, dioxane, ether or THF, preferably dioxane. The reaction is typically run at a temperature from about -10°C to about 50°C, preferably about 25°C, for about 0.5 to about 24 hours.

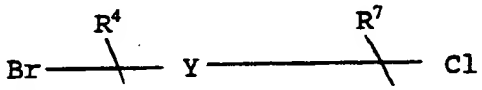
Reduction of the compound of formula X so formed yields a compound of the formula IB having the same stereochemistry. This reaction is carried out in the same manner as described above in the discussion of scheme 1 for preparing compounds of the formula IA from compounds of the formula VI, and for preparing compounds of the formula IC from compounds of the formula VII.

Scheme 3 illustrates a method of preparing compounds of the formula ID. Formula ID represents compounds of the formula I wherein each of R^1 and R^6 are hydrogen, m is 0 and n is 2, 3 or 4. This group of compounds includes those of the formula IA. The method of scheme 3 can be used to prepare the pure 2S,3S enantiomer, the pure 2R,3R enantiomer, or a racemic mixture of a compound of the formula ID, depending on whether the starting material is, respectively, the R-enantiomer, the S-enantiomer, or a racemic mixture of the starting material of formula XI. Also, because formula ID includes compounds of the formula IA, the method of scheme 3 can be used to prepare compounds of the formula IA wherein R^4 is attached to the "6" position of the nitrogen containing ring. The method of scheme 3 can also be used to prepare compounds of the formula ID wherein R^2 is benzhydryl.

Referring to scheme 3, compounds of the formula ID may be prepared as follows. The pure R-enantiomer, S-enantiomer or a racemic mixture of a compound of the formula XI is reacted with a nitrogen-protecting reagent such as t-butyldimethylsilyl chloride (TBDMS-Cl), t-butyldimethylsilyl triflate (TBDMS-OTf) or benzyl bromide/t-butoxide, preferably TBDMS-Cl, to form a compound of the formula XII. This reaction is typically carried out

in a polar solvent such as DMF or triethylamine, preferably triethylamine, at a temperature of from about 0 to about 140°C. Room temperature is preferred.

The above reaction is followed by a stereospecific alkylation of the compound of formula XII to form the trans stereoisomer of a compound of the formula XIII. First, the compound of formula XII is reacted with lithium diethylamide in a polar solvent such as ether or THF, preferably THF, at a temperature from about -100°C to about room temperature, preferably about -78°C. Then, a compound of the formula



is added to the reaction mixture to produce the trans isomer of a compound of the formula XIII. Simultaneous removal of the TBDMS group and cleavage of the ß-lactam using concentrated sulfuric or perchloric acid, preferably sulfuric acid, in a polar solent such as methanol or ethanol, preferably methanol, yields a compound of the formula XIV. This reaction is typically carried out at a temperature from about room temperature to about 150°C, preferably at about the reflux temperature of the solvent, for about 0.5 to about 16 hours.

The cyclization of the compound of formula XIV to produce a compound of the formula XV is accomplished by heating the crude product of formula XIV from the foregoing reaction at a temperature from about 80°C to about 140°C, preferably at about 100°C, for about 5 minutes to about 2 days, preferably for about 15 minutes, in a high boiling solvent such as DMF or toluene, preferably in DMF. Generally, this reaction is conducted in the presence of sodium iodide and sodium bicarbonate. In the compound of formula XV produced by this reaction, R^2 and $-COOCH_3$ are cis to each other.

The compound of formula XV is then treated with benzylchloroformate in a polar solvent such as water, water/acetone, chloroform, dichloroethane or ethyl acetate,

in the presence of a base such as triethylamine or sodium bicarbonate, to yield the N-carbobenzyloxy piperidine (N-Cbz piperidine) of formula XVI having the same stereochemistry (i.e., wherein R^2 and $-COOCH_3$ are in the cis configuration). This reaction may be carried out at temperatures from about 0°C to about 100°C, preferably about 25°C, for about 5 minutes to 18 hours. Treatment of the compound of formula XVI so formed with about 5 equivalents each of trimethyl aluminum and ammonium chloride in a nonpolar solvent such as benzene or toluene for about 0.5 to about 16 hours yields a compound of the formula XVII having the same stereochemistry. Reaction temperatures may range from about room temperature to about 100°C, with about 50°C being preferred.

The conversion of the carboxamide group of the compound of formula XVII to form a compound of the formula XVIII having the same stereochemistry may be accomplished by a Hoffmann degradation using reagents such as bromine/sodium methoxide in methanol, lead tetraacetate in t-butyl alcohol, tin (IV) chloride, iodobenzene bis(trifluoroacetate) in aqueous acetonitrile, sodium bromide or benzyltrimethyl ammonium tribromide. Preferably, the compound of formula XVII is treated with lead tetraacetate in t-butanol. This reaction is typically carried out at a temperature from about room temperature to the reflux temperature of the solvent, preferably at the reflux temperature, for about 15 minutes to about 10 hours, preferably for about 3 to about 5 hours. Reaction of the compound of formula XVIII with an acid such as hydrochloric acid, trifluroacetic acid or perchloric acid yields a compound of the formula XIX having the same stereochemistry. The solvent is typically a polar solvent such as methylene chloride, dioxane, ether or THF, preferably dioxane. This reaction is typically carried out at a temperature from about -10 to about 50°C, preferably at about 25°C, for about 0.5 to 24 hours.

Reductive amination of the compound of the formula XIX from the above step with sodium cyanoborohydride or sodium triacetoxyborohydride and a compound of the formula R^3CHO yields a compound of the formula XX having the same stereochemistry. This reaction is generally carried out in a polar solvent such as acetic acid or a lower alkanol, at a temperature from about 0 to about 50°C. Methanol is the preferred solvent and about 25°C is the preferred temperature. It is also preferred that the pH of the reaction mixture be about 4 to about 5.

The compound of formula XX is converted into a compound of the formula ID wherein R^2 and the amino group are cis to each other by reacting it with ammonium formate in the presence of palladium on charcoal (e.g. 10% palladium on charcoal). Typically, a polar solvent such as ethyl acetate or a lower alkanol is used, and the reaction is run at a temperature from about room temperature to about 150°C for about 0.5 to about 24 hours. Preferably, the reaction is conducted in ethanol at room temperature for about 3 to about 24 hours.

The trans isomer of a compound of the formula ID (i.e., one wherein the amino group and R^2 are trans to each other) may be prepared by the same procedure described above for obtaining the cis isomer, with the following modification. To prepare the trans isomer, either the compound of formula XV or the compound of formula XVI, after its formation as described above, is treated with potassium t-butoxide or a lithium dialkylamide. The solvent for this reaction is generally a polar solvent such as THF or ether, and the reaction is generally conducted at a temperature from about -78°C to room temperature, preferably at about 0°C, for about 5 minutes to about 10 hours.

An alternate method of preparing compounds of the formula ID wherein R^2 is benzhydryl is described in Examples 21-26.

Scheme 4 illustrates a preferred method of preparing compounds of the formula ID wherein n is 2. According to this method, a compound of the formula XXI is treated with hydrogen gas in the presence of a metal catalyst such a palladium on charcoal, platinum on charcoal or platinum dioxide, preferably palladium on charcoal, and in the presence of an acid such as trifluroacetic acid or hydrochloric acid, to produce a compound of the formula XXII. A polar inert solvent is generally used. The preferred solvent is ethanol. This reaction is typically carried out at a pressure of about 1.5 atm to about 5 atm, preferably at about 3.0 atm, at a temperature from about 0°C-60°C, preferably at about 25°C. The compound of formula XXII so formed is then converted to a compound of the formula ID by the procedure illustrated in scheme 3 and described above.

Enantiomerically pure compounds of the formula IC (i.e., compounds of the formula ID wherein R^1 is (C_1-C_6) alkyl rather than hydrogen) may be prepared as follows. A compound of the formula XX, prepared as described above, is alkylated by reacting it with a compound of the formula R^1X, wherein X is halo. This reaction is usually conducted in the presence of a base such as triethylamine or potassium t-butoxide, in a polar solvent such as methylene chloride or dichloroethane, and at a temperature from about room temperature to about 200°C. Preferably, the reaction is conducted at the reflux temperature in methylene chloride in the presence of triethylamine. The alkylated product, which has the same stereochemistry as the starting material of formula XX, is then converted to a compound of the formula IC having the same stereochemistry, by reacting it with ammonium formate in the presence of palladium on charcoal (e.g. 10% palladium on charcoal). Typically, a polar solvent such as ethyl acetate or a lower alkanol is used, and the reaction is run at a temperature from about room temperature to about 80°C for about 3 to about 24

hours. The reaction is preferably conducted in ethanol at room temperature for about 0.5 to about 24 hours.

Enantiomerically pure compounds of the formula IB may be prepared by reacting the analogous compound of the formula ID, having the same stereochemistry, with a compound of the formula $R^6-(CH_2)_m-X$, wherein X is halo or mesylate. In each of $X-(CH_2)_m-R^6$ and $CH_3SO_2O-(CH_2)_m-R^6$, one of the carbons of said $(CH_2)_m$ may optionally be substituted with R^8 and one of the carbon-carbon single bonds of said $(CH_2)_m$ may optionally be replaced with a carbon-carbon double bond. The reaction is performed in the same manner as described above for converting compounds of the formula IA into compounds of the formula IB.

Compounds having the formula IA wherein R^4, R^5 and R^7 are each hydrogen and R^2 is phenyl may be prepared, alternatively, by reductive amination of 3-amino-2-phenylpiperidine, using the appropriate aldehyde of the formula R^3CHO, as described above for converting compounds of the formula V to the corresponding compounds of the formula VI. The starting material for this reaction, 3-amino-2-phenylpiperidine, may be prepared by hydrogenolysis of 3-(2-methoxybenzylamino)-2-phenylpiperidine. The hydrogenolysis reaction is usually carried out using a catalyst such as palladium on carbon or palladium hydroxide, in an inert solvent such as acetic acid or an alcoholic solvent, at a temperature from about 0°C to about 50°C. It is preferably carrier out at about room temperature in a methanol/ethanol solvent. It is also preferable to conduct this reaction in the presence of a mineral acid such as hydrochloric or sulfuric acid.

The above two step process for preparing compounds of the formula IA wherein R^4, R^5 and R^7 are each hydrogen and R^2 is phenyl from 3-(2-methoxybenzylamino)-2-phenylpiperidine preserves the stereochemistry at the "2" and "3" positions of the piperidine ring. It therefore may be used to produce either pure enantiomer or a racemic mixture of the product of formula IA from a sample of 3-(2-methoxybenzylamino)-2-

phenylpiperidine having the same stereochemistry. Similarly, the first step of the above process may be used to produce either pure enantiomer or a racemic mixture of 3-amino-2-phenylpiperidine.

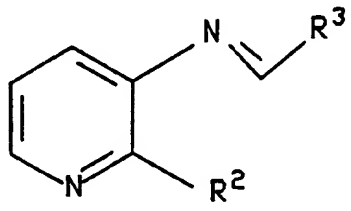
An alternative method of preparing racemic 3-amino-2-phenylpiperidine is by reducing 3-amino-2-phenylpyridine. This reduction is generally accomplished using either sodium in alcohol, lithium aluminum hydride/aluminum trichloride, electrolytic reduction or hydrogen in the presence of a metal catalyst. The reduction with sodium is generally conducted in a boiling alcohol, preferably butanol, at a temperature from about 20°C to about the reflux temperature of the solvent, preferably at about 120°C. The reduction with lithium aluminum hydride/aluminum trichloride is usually carried out in ether, THF or dimethoxyethane, preferably ether, at a temperature from about 25°C to about 100°C, preferably at about room temperature. The electrolytic reduction is conducted, preferably, at room temperature, but temperatures from about 10°C to about 60°C are also suitable.

Hydrogenation in the presence of a metal catalyst is the preferred method of reduction. Suitable hydrogenation catalysts include palladium, platinum, nickel and rhodium. The preferred catalyst for hydrogenation is platinum oxide. The reaction temperature may range from about 10°C to about 50°C, with about 25°C being preferred. The hydrogenation is generally carried out at a pressure from about 1.5 to about 4 atmospheres, preferably at about 3.0 atmospheres.

Compounds of the formula IA wherein R^4, R^5 and R^7 are each hydrogen and R^2 is phenyl may also be prepared by the following method. According to this method, 3-amino-2-phenylpyridine is first converted into the pyridine analog of the desired piperidine of the formula IA by reacting it with the appropriate compound of the formula R^3CHO or R^3CH_2X wherein X is a leaving group (e.g. chloro, bromo, iodo, mesylate or tosylate).

The reaction of 3-amino-2-phenylpyridine with a compound of the formula R^3CHO to produce the pyridine analog of the piperidine of formula IA is typically carried out in the presence of a reducing agent such as sodium cyanoborohydride, sodium triacetoxyborohydride, sodium borohydride, hydrogen and a metal catalyst, zinc and hydrochloric acid, or formic acid at a temperature from about -60°C to about 50°C. Suitable reaction inert solvents for this reaction include lower alcohols (e.g., methanol, ethanol and isopropanol), acetic acid and THF. Preferably, the solvent is methanol, the temperature is about 25°C, and the reducing agent is sodium cyanoborohydride.

Alternatively, the reaction of 3-amino-2-phenylpyridine with a compound of the formula R^3CHO may be carried out in the presence of a drying agent or using an apparatus designed to remove azeotropically the water generated, to produce an imine of the formula



which is then reacted with a reducing agent as described above, preferably with sodium triacetoxyborohydride at about room temperature. The preparation of the imine is generally carried out in a reaction inert solvent such as benzene, xylene or toluene, preferably toluene, at a temperature from about 25°C to about 110°C, preferably at about the reflux temperature of the solvent. Suitable drying agents/solvent systems include titanium tetrachloride/dichloromethane and molecular sieves/THF. Titanium tetrachloride/dichloromethane is preferred.

The reaction of 3-amino-2-phenylpyridine with a compound of the formula R^3CH_2X is typically carried out in a reaction inert solvent such as dichloromethane or THF,

preferably dichloromethane, at a temperature from about 0°C to about 60°C, preferably at about 25°C.

The pyridine so formed is then reduced to form the desired piperidine of formula IA by the procedure described above for reducing 3-amino-2-phenylpyridine.

Compounds of the formula IB may be prepared, in addition to the method illustrated in scheme 1 and described above, from other compounds of the formula IB by modifying the R^6 and R^8 containing side chain. The appropriate modifications may be accomplished using methods well known to those skilled in the art. Some of these modifications are described in Examples 93-104.

The preparation of other compounds of the formula I and the Group II compounds not specifically described in the foregoing experimental section can be accomplished using combinations of the reactions described above that will be apparent to those skilled in the art.

Methods of preparing the Group II compounds are also exemplified in Examples 5-12 and 14-28.

In each of the reactions discussed or illustrated in schemes 1 to 4 above, pressure is not critical unless otherwise indicated. Pressures from about 0.5 atmospheres to about 5 atmospheres are generally acceptable, and ambient pressure, i.e. about 1 atmosphere, is preferred as a matter of convenience.

The novel compounds of the formula I and the Group II compounds, and the pharmaceutically acceptable salts thereof, are useful as substance P antagonists, i.e., they possess the ability to antagonize the effects of substance P at its receptor site in mammals, and therefore they are able to function as therapeutic agents in the treatment of the aforementioned disorders and diseases in an afflicted mammal.

The compounds of the formula I and the Group II compounds which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be

pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I (or a Group II compound) from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained.

The compounds of formula I and the Group II compounds and their pharmaceutically acceptable salts exhibit substance P receptor-binding activity and therefore are of value in the treatment and prevention of a wide variety of clinical conditions the treatment or prevention of which are effected or facilitated by a decrease in substance P mediated neurotransmission. Such conditions include inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypertension, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and

rheumatic diseases such as fibrositis. Hence, these compounds are readily adapted to therapeutic use as substance P antagonists for the control and/or treatment of any of the aforesaid clinical conditions in mammals, including humans.

The compounds of the formula I and the Group II compounds and the pharmaceutically acceptable salts thereof can be administered via either the oral, parenteral or topical routes. In general, these compounds are most desirably administered in dosages ranging from about 5.0 mg up to about 1500 mg per day, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 0.07 mg to about 21 mg per kg of body weight per day is most desirably employed. Variations may nevertheless occur depending upon the species of animal being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

The compounds of the formula I and the Group II compounds may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by either of the three routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the novel therapeutic agents of this invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies,

powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the compounds of formula I and the Group II compounds (i.e., the therapeutically-effective compounds of this invention) are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8) if necessary and

the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

Additionally, it is also possible to administer the compounds of the present invention topically when treating inflammatory conditions of the skin and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

The activity of the compounds of the present invention as substance P antagonists is determined by their ability to inhibit the binding of substance P at its receptor sites in bovine caudate tissue, employing radioactive ligands to visualize the tachykinin receptors by means of autoradiography. The substance P antagonizing activity of the herein described compounds may be evaluated by using the standard assay procedure described by M. A. Cascieri et al., as reported in the Journal of Biological Chemistry, Vol. 258, p. 5158 (1983). This method essentially involves determining the concentration of the individual compound required to reduce by 50% the amount of radiolabelled substance P ligands at their receptor sites in said isolated cow tissues, thereby affording characteristic IC_{50} values for each compound tested.

In this procedure, bovine caudate tissue is removed from a -70°C freezer and homogenized in 50 volumes (w./v.) of an ice-cold 50 mM Tris (i.e., trimethamine which is 2-amino-2-hydroxymethyl-1,3-propanediol) hydrochloride buffer having a pH of 7.7. The homogenate is centrifuged at 30,000 x G for a period of 20 minutes. The pellet is resuspended in 50 volumes of Tris buffer, rehomogenized and then recentrifuged at 30,000 x G for another twenty- minute period. The pellet is then resuspended in 40 volumes of

ice-cold 50 mM Tris buffer (pH 7.7) containing 2 mM of calcium chloride, 2 mM of magnesium chloride, 40 g/ml of bacitracin, 4μg/ml of leupeptin, 2μg of chymostatin and 200 g/ml of bovine serum albumin. This step completes the production of the tissue preparation.

The radioligand binding procedure is then carried out in the following manner, viz., by initiating the reaction via the addition of 100 μl of the test compound made up to a concentration of 1 μM, followed by the addition of 100 μl of radioactive ligand made up to a final concentration 0.5 mM and then finally by the addition of 800 μl of the tissue preparation produced as described above. The final volume is thus 1.0 ml, and the reaction mixture is next vortexed and incubated at room temperature (ca. 20°C) for a period of 20 minutes. The tubes are then filtered using a cell harvester, and the glass fiber filters (Whatman GF/B) are washed four times with 50 mM of Tris buffer (pH 7.7), with the filters having previously been presoaked for a period of two hours prior to the filtering procedure. Radioactivity is then determined in a Beta counter at 53% counting efficiency, and the IC_{50} values are calculated by using standard statistical methods.

The anti-psychotic activity of the compounds of the present invention as neuroleptic agents for the control of various psychotic disorders is determined primarily by a study of their ability to suppress substance P-induced or substance P agonist induced hypermotility in guinea pigs. This study is carried out by first dosing the guinea pigs with a control compound or with an appropriate test compound of the present invention, then injecting the guinea pigs with substance P or a substance P agonist by intracerebral administration via canula and thereafter measuring their individual locomotor response to said stimulus.

The present invention is illustrated by the following examples. It will be understood, however, that the

invention is not limited to the specific details of these examples.

EXAMPLE 1

Cis-3-(2-methoxybenzylamino)-2-phenylpiperidine

A. 2-Oxo-5-oximino-6-phenylpiperidine

To a stirred solution of trans-5-nitro-2-oxo-6-phenylpiperidine (27.0 gms, 122.6 mmole) in 1:1 methylene chloride:methanol was added potassium tert. butoxide (135 mmole, 15.1 gms) at 25°C. This reaction mixture was cooled to -78°C and ozone gas was bubbled until (3 hrs) TLC (10% methanol in methylene chloride) indicated no starting material. The reaction mixture was then purged with nitrogen to remove excess ozone, and was then treated with dimethyl sulfide (60 ml) at -78°C. After warming to room temperature in 30 min., it was treated with an aqueous solution of hydroxylamine (85.2 gms, 1.22 mole) and sodium acetate (50.3 gms, 613 mmole) in water (220 ml). After stirring for 16 hrs, the volatile material was removed using a rotary evaporator. The residue was poured into 1.2 liters of cold water and stirred for 30 min. The precipitated solid was filtered to give 2-oxo-3-oxamino-6-phenylpiperidine (14.0 gms, 56.0%). M.p. 178°C.

^{1}H NMR (DMSO-d_6, 300 MHz, δ): 2.04-2.22 (2H, m); 2.4-2.42 (1H, m), 2.71 (1H, dt, J = 8, 16 Hz); 5.02 (1H, d, J = 4 Hz), 7.28-7.41 (5H, m); 8.35 (1H, d, J = 4 Hz); 10.99 (1H, s).

TLC: (90:10 - methylene chloride:methanol) R_f=0.54.

B. Cis-5-(2-methoxybenzylamino)-2-oxo-6-phenyl-piperidine:

2-Oxo-5-oximino-6-phenylpiperidine (28.2 gms, 138 mmole) was dissolved (heating on steam bath is necessary to achieve a clear solution) in ethanol (500 ml) containing methanol (50 ml). Neutral Raney Ni (80 gms) was added and the mixture was shaken on a Parr shaker under hydrogen (40 psi). After 18 hours, the reaction mixture was filtered through diatomaceous earth (Celite (Trademark)) which was thoroughly washed with methanol. The organic solvents were

removed using a rotary evaporator to afford an oil which solidified on standing (26.2 gms, 100%). ^{1}H-NMR indicated it to be a 3:1 mixture of cis-5-amino-2-oxo-6-phenyl-piperidine and trans-5-amino-2-oxo-6-phenylpiperidine, respectively. This mixture was dissolved in methanol (345 ml) and the pH was adjusted to 5 with saturated methanolic hydrochloric acid. Four Å sieves (55 gms), sodium cyanoborohydride (138 mmole) and o-methoxy-benzaldehyde (22.5 gms, 165 mmole) were added to the system. Stirring was continued (4 hours) until the reaction was complete as indicated by TLC. The reaction mixture was filtered through diatomaceous earth (Celite (trademark)) and the filtrate was concentrated using a rotary evaporator. The residue was suspended in water and the pH made basic. The aqueous phase was extracted with methylene chloride (4 x 200 ml) washed with water, brine, and then dried (anhyd. magnesium sulfate) and concentrated to give an oil (47.0 gms) which was flash chromatographed. Elution with 3% methanol in methylene chloride afforded a white solid (19.6 gms, m.p. 122°C).

^{1}H NMR ($CDCl_3$) δ1.81-1.96 (1H, m); 2.0-2.18 (1H, m); 2.4 (1H, dt, J = 4.5, 16 Hz); 2.75 (1H, ddd, J = 6.5, 10.5 16 Hz); 3.48 (3H, s); 3.54 (1H, dd, J = 13.8 Hz); 3.76 (1H, dd, J = 13.8 Hz); 4.72 (1H, d, J = 4Hz); 5.72 (1H, bs); 6.71 (1H, d, J = 8 Hz); 6.8 (1H, t, J = 6.8 Hz); 7.04 (1H, dd, J = 1.8, 7.2 Hz); 7.17 (1H, dt, J = 1.6, 8.2 Hz); 7.2-7.44 (5H, m).

HRMS: Calculated for $C_{19}H_{22}N_2O_2$: 310.1682. Found: 310.1649.

TLC: (90:10 - methylene chloride:methanol) R_f = 0.47.

C. <u>Cis-3-(2-methoxybenzylamino)-2-phenylpiperidine</u>

Borane dimethylsulfide in tetrahydrofuran (2M, 158 ml, 315 mmole) was added to a solution of cis-5-(2-methoxybenzylamino)-2-oxo-6-phenylpiperidine (19.6 g, 63.0 mmole) in tetrahydrofuran (500 ml) under nitrogen and the reaction mixture was heated at reflux for 18 hours. At the end of this period, the reaction mixture was cooled and

the excess borane dimethylsulfide was cautiously decomposed by dropwise addition of methanol. The contents of the reaction mixture were then concentrated under vacuum. Ethanol (500 ml) and powdered potassium carbonate (17.5 g, 126 mmole) were added to the residue and the reaction mixture was heated at reflux (18 hours). Then the reaction mixture was concentrated under vacuum and the residue was extracted with methylene chloride (4 x 250ml) and dried (anhydrous magnesium sulfate). The organic solvents were removed under vacuum to afford a residue which was dissolved in a minimum amount of methylene chloride. To this solution was added excess hydrochloric acid/ether, thus precipitating the dihydrochloride salt of cis-3-(2-methoxybenzylamino)-2-phenylpiperidine, which was isolated by filtration. This was heated at reflux in chloroform (400 ml) for 3 hours and filtered to give the essentially pure hydrochloride salt of the title compound (22.4 gms, m.p. 245°C, 96%), which was crystallized from a mixture of hot methanol-ethanol to afford a white crystalline solid (19.2 gms, 83%).

M.p. 255°C (HCl salt). ^{1}H-NMR ($CDCl_3$, free base) δ 7.1-7.3 (6H, m); 6.97 (1H, dd, J = 1.7, 7.4 Hz); 6.79 (1H, bt, J = 7.4 Hz); 6.66 (1H, d, J = 8.2 Hz); 3.87 (1H, d, J = 2.3 Hz); 3.67 (1H, d, J = 11.4 Hz): 3.44 (3H, s); 3.4 (1H, d, J = 14 Hz); 3.22-3.3 (1H, bd, J = 12.2 Hz); 2.72-2.86 (2H, m); 2.09-2.19 (1H, bd, J = 13.7 Hz); 1.84-2.01 (1H, dt, J = 4.0, 13.0 Hz); 1.53-1.7 (1H, dt, J = 3.5, 13.4 Hz); 1.33-1.45 (1H, bd, J = 12.5 Hz). ^{13}C-NMR ($CDCl_3$, free base) δ 157.6, 142.5, 129.6, 128.3, 128.2, 127.8, 126.5, 126.3, 120.0, 109.8, 64.0, 54.8, 54.7, 47.8, 46.7, 28.2, 20.4. HRMS Calcd. for $C_{19}H_{24}N_2O$: 296.1886. Found: 296.1904.

TLC : (90:10 - methylene chloride:methanol) R_f = 0.39.

EXAMPLE 2

Cis-1-allyl-3-(2-methoxybenzylamino)-2-phenylpiperidine

Under a nitrogen atmosphere, in a round-bottom flask, were placed 60 mg (0.2 mmol) of the title compound of

Example 1 and 0.2 ml of methylene chloride. To this system were added 28 μl (0.2 mmol) of triethylamine and 17.5 μl (0.2 mmol) of allyl bromide, and the reaction mixture was stirred at room temperature overnight. The mixture was partitioned between methylene chloride and saturated aqueous sodium bicarbonate, the layers were separated, and the aqueous phase was extracted with three portions of methylene chloride. The combined organic fractions were dried (sodium sulfate) and concentrated with a rotary evaporator. The crude material was purified by flash column chromatography to obtain 26 mg of the title compound.

^{1}H NMR ($CDCl_3$) δ 7.20 (m, 5H), 7.03 (t, 1H, J = 6 Hz), 6.79 (d, 1H, J = 6 Hz), 6.88 (t, 1H, J = 6 Hz), 6.57 (d, 1H, J = 6 Hz), 5.78 (m, 1H), 4.94 (m, 2H), 3.62 (d, 1H, J = 12 Hz), 3.40 (s, 3H), 3.32 (d, 1H, J = 12 Hz), 3.26 (d, 1H, J = 2 Hz), 3.18 (m, 1H), 2.56 (m, 1H), 2.36 (m, 1H), 1.98 (m, 3H), 1.68 (m, 1H), 1.38 (m, 2H).

HRMS: Calcd for $C_{22}H_{28}N_2O$: 336.2202. Found: 336.2216.

EXAMPLE 3

(+)-(2S,3S)-3-(2,5-Dimethoxybenzyl)amino-2-phenylpiperidine

Under a nitrogen atmosphere in a round-bottom flask were placed 600 mg (3.4 mmol) of (+)-(2S,3S)-3-amino-2-phenylpiperidine, 8 ml of acetic acid and 622 mg (3.7 mmol) of 2,5-dimethoxybenzaldehyde, and the mixture was stirred for 30 minutes. To the system was added 1.58 g (7.5 mmol) of sodium triacetoxyborohydride, and the mixture was stirred at room temperature overnight. The mixture was concentrated, basified with 1M aqueous sodium hydroxide and extracted with methylene chloride. The methylene chloride extracts were washed with water and extracted with 1M aqueous hydrocloric acid. The hydrochloric acid extracts were basified with 1M aqueous sodium hydroxide and extracted with methylene chloride. The methylene chloride extracts were dried (sodium sulfate) and concentated to obtain 528 mg of colorless oil. The oil was dissolved in methylene

chloride, and ether saturated with hydrogen chloride was added to the solution. The resulting white solid was collected by filtration and stirred in isopropanol at 60°C for 2 hours. Filtration afforded 414 mg of the title compound as its hydrochloride. Additional material (400 mg) was obtained by extracting the initial basic layer with additional methylene chloride, drying (sodium sulfate) and concentration. $[\alpha]_D$ (HCl salt) = + 60.5° (c=0.58, CH_3OH).

^1H NMR ($CDCl_3$) δ 1.38 (m, 1H), 1.58 (m, 1H), 1.88 (m, 1H), 2.13 (m, 1H), 2.78 (m, 2H), 3.25 (m, 1H), 3.36 (d, 1H, J=18), 3.44 (s, 3H), 3.62 (d, 1H, J=18), 3.72 (s, 3H), 3.88 (d, 1H, J=3), 6.62 (m, 3H), 7.24 (m, 5H). Mass spectrum: m/z 326 (parent). Calc'd for $C_{20}H_{26}N_2O_2 \cdot 2HCl \cdot 0.25H_2O$: C, 59.48; H, 7.11; N, 6.93. Found: C, 59.33; H, 6.91; N, 7.23.

EXAMPLE 4

(2S,3S)-3-(2-Methoxybenzyl)amino-1-[4-(2-naphthamido-but-1-yl)]-2-phenylpiperidine

Under a nitrogen atmosphere in a round-bottom flask were placed 100 mg (0.27 mmol) of the title compound of Example 94 and 0.5 ml of methylene chloride, and the system was cooled in an ice bath. To the system was added 38 µl (0.27 mmol) of 2-naphthoyl chloride, and the mixture was stirred for 20 minutes. The mixture was poured into saturated aqueous sodium bicarbonate and extracted with chloroform. The chloroform extracts were dried (sodium sulfate) and concentrated to obtain 150 mg of an oil. The crude product was purified by flash column chromatography (6 g of silica gel) using 1:10 methanol/chloroform as the eluant to obtain 71 mg of the title compound, which was converted to its hydrochloride salt.

M.p. 105-107°C (dec.)

^1H NMR ($CDCl_3$) δ 1.50 (m, 6H), 1.70 (m, 2H), 2.04 (m, 3H), 2.60 (m, 2H), 3.22 (m, 1H), 3.30 (d, 1H, J=1), 3.40 (m, 5H), 3.68 (d, 1H, J=15), 6.28 (br s, 1H), 6.61 (d, 1H, J=9), 6.72 (t, 1H, J=6), 6.84 (d, 1H, J=6), 7.08 (t, 1H, J=9), 7.26 (m, 5H), 7.52 (m, 2H), 7.82 (m, 4H), 8.22 (s, 1H). Mass spectrum: m/z 521 (parent).

EXAMPLE 5

(2S,3S)-3-(4,5-Difluoro-2-methoxybenzyl)amino-2-phenylpiperidine

The title compound was prepared by a procedure similar to that described in Example 3.

^{1}H NMR ($CDCl_3$) δ 1.36 (m, 1H), 1.55 (m, 1H), 1.84 (m, 1H), 2.02 (m, 1H), 2.72 (m, 2H), 3.20 (m, 1H), 3.26 (d, 1H, J=14), 3.42 (s, 3H), 3.52 (d, 1H, J=14), 3.84 (d, 1H, J=3), 6.42 (dd, 1H, J=6, 12), 6.70 (dd, 1H, J=8, 10), 7.20 (m, 5H).

Anal. Calc'd for $C_{19}H_{22}F_2N_2O \cdot 2HCl \cdot 0.55H_2O$: C, 54.96; H, 6.09; N, 6.75. Found: C, 54.65; H, 5.69; N, 6.74.

EXAMPLE 6

(2S,3S)-3-(2-Cyclopentyloxy-5-methoxybenzyl)amino-2-phenylpiperidine

The title compound was prepared by a procedure similar to that described in Example 3.

M.p. 217-219°C (HCl salt).

^{1}H NMR ($CDCl_3$) δ 1.66 (m, 13H), 2.14 (m, 1H), 2.82 (dt, 2H, J=12, 3), 2.92 (m, 1H), 3.14 (m, 2H), 3.54 (d, 1H, J=15), 3.72 (s, 3H), 3.90 (d, 1H, J=15), 4.50 (m, 1H), 6.64 (m, 3H), 7.30 (m, 5H).

HRMS Calc'd for $C_{24}H_{32}N_2O_2$: 380.2456. Found: 380.2457.

Anal. Calc'd for $C_{24}H_{32}N_2O_2 \cdot 2HCl \cdot H_2O$: C, 60.14; H, 7.70; N, 5.94. Found: C, 61.05; H, 7.67; N, 5.92.

EXAMPLE 7

(2S,3S)-3-(5-sec-Butyl-2-methoxybenzyl)amino-2-phenylpiperidine

The title compound was prepared by a procedure similar to that described in Example 3.

M.p. 260-263°C (HCl salt).

^{1}H NMR ($CDCl_3$) δ 0.8 (2t, 3H, J=6), 1.16 (2d, 3H, J=7), 1.5 (m, 4H), 1.9 (m, 1H), 2.12 (m, 1H), 2.46 (m, 1H), 2.8 (m, 3H), 3.28 (m, 1H), 3.42 (d, 1H, J=15), 3.44 (s, 3H), 3.66 (d, 1H, J=15), 3.90 (d, 1H, J=3), 6.60 (d, 1H, J=10), 6.78 (broad s, 1H), 6.92 (d, 1H, J=10), 7.3 (m, 5H).

HRMS Calc'd for $C_{23}H_{32}N_2O$: 352.2507. Found: 352.2525.

Anal. Calc'd for $C_{23}H_{32}N_2O \cdot 2HCl \cdot H_2O$: C, 62.29; H, 8.18; N, 6.32. Found C, 62.95; H, 7.62; N, 6.61.

EXAMPLE 8

(2S,3S)-3-(5-tert-Butyl-2-methoxybenzyl)amino-2-phenylpiperidine

The title compound was prepared by a procedure similar to that described in Example 3.

M.p. 262-264°C (HCl salt).

^1H NMR ($CDCl_3$) δ 1.22 (s, 9H), 1.38 (m, 2H), 1.90 (m, 1H), 2.14 (m, 1H), 2.80 (m, 2H), 3.26 (m, 1H), 3.36 (d, 1H, J=15), 3.44 (s, 3H), 3.62 (d, 1H, J=15), 3.86 (d, 1H, J=3), 6.60 (d, 1H, J=10), 7.00 (d, 1H, J=3), 7.12 (m, 1H), 7.26 (m, 5H).

HRMS Calc'd for $C_{23}H_{32}N_2O$: 352.2507. Found: 352.2512.

Anal. Calc'd for $C_{23}H_{32}N_2O \cdot 2HCl \cdot 0.5H_2O$: C, 63.58; H, 8.12; N, 6.45. Found C, 63.75; H, 8.00; N, 6.42.

EXAMPLE 9

(2S,3S)-3-(2-Cyclopentyloxybenzyl)amino-2-phenylpiperidine

The title compound was prepared by a procedure similar to that described in Example 3.

M.p. 230-232°C (HCl salt).

^1H NMR ($CDCl_3$) δ 1.75 (m, 13H), 2.14 (m, 1H), 2.80 (dt, 2H, J=12, 3), 2.90 (m, 1H), 3.28 (m, 1H), 3.36 (d, 1H, J=15), 3.60 (d, 1H, J=15), 3.88 (braod s, 1H), 4.58 (m, 1H), 6.74 (m, 2H), 6.84 (d, 1H, J=10), 7.12 (m, 1H), 7.30 (m, 5H).

HRMS Calc'd for $C_{23}H_{40}N_2O$: 350.2351. Found: 350.2332.

Anal. Calc'd for $C_{23}H_{30}N_2O \cdot 2HCl \cdot 2H_2O$: C, 60.12; H, 7.33; N, 6.10. Found C, 59.10; H, 7.19; N, 6.09.

EXAMPLE 10

(2S,3S)-3-(2-Acetamidobenzyl)amino-2-phenylpiperidine

The title compound was prepared by a procedure similar to that described in Example 3.

M.p. 187-195°C (HCl salt).

^1H NMR ($CDCl_3$) δ 1.52 (m, 1H), 1.61 (s, 3H), 1.70 (m, 1H), 2.10 (m, 2H), 2.80 (m, 2H), 3.18 (m, 1H), 3.32 (d, 1H,

J=16), 3.54 (d, 1H, J=16), 3.89 (d, 1H, J=3), 6.88 (m, 2H), 7.26 (m, 7H).

HRMS Calc'd for $C_{20}H_{25}N_3O$: 323.1997. Found: 323.1972.

EXAMPLE 11

(2S,3S)-3-(5-Ethyl-2-methoxybenzyl)amino-2-phenylpiperidine hydrochloride

The title compound was prepared by a procedure similar to that described in Example 3.

^1H NMR (free base, $CDCl_3$) δ 1.16 (t, 3H, J=9), 1.36 (m, 1H), 1.57 (m, 1H), 1.88 (m, 1H), 2.12 (m, 1H), 2.48 (q, 2H), 2.76 (m, 2H), 3.24 (m, 1H), 3.38 (m, 4H), 3.60 (d, 1H, J=12), 3.86 (d, 1H, J=3), 6.57 (d, 1H, J=6), 6.74 (d, 1H, J=3), 6.92 (dd, 1H, J=3,6), 7.24 (m, 5H).

HRMS Calc'd for $C_{21}H_{28}N_2O$: 324.2202. Found: 324.2184.

EXAMPLE 12

(2S,3S)-3-(4-Amino-5-chloro-2-methoxybenzyl)amino-2-phenylpiperidine hydrochloride

The title compound was prepared by a procedure similar to that described in Example 3.

M.p. 200-203°C (dec).

^1H NMR (free base, $CDCl_3$) δ 1.35 (m, 1H), 1.56 (m, 1H), 1.86 (m, 1H), 2.05 (m, 1H), 2.75 (m, 2H), 3.22 (m, 2H), 3.36 (s, 3H), 3.48 (d, 1H, J=12), 3.84 (d, 1H, J=2), 6.08 (s, 1H), 6.78 (s, 1H), 7.24 (m, 5H).

HRMS Calc'd for $C_{19}H_{24}ClN_3O$: 345.1604. Found: 345.1589.

EXAMPLE 13

(2S,3S)-3-(2-Methoxy-5-phenylbenzyl)amino-2-phenylpiperidine hydrochloride

The title compound was prepared by a procedure similar to that described in Example 3.

M.p. 238-239°C (dec).

^1H NMR (free base, $CDCl_3$) δ 1.38 (m, 1H), 1.60 (m, 1H), 1.88 (m, 1H), 2.12 (m, 1H), 2.80 (m, 2H), 3.23 (m, 1H), 3.45 (m, 4H), 3.70 (d, 1H, J=12), 3.86 (d, 1H, J=3), 6.70 (d, 1H, J=6), 7.34 (m, 12H).

HRMS Calc'd for $C_{25}H_{28}N_2O$: 372.2197. Found: 372.2172.

EXAMPLE 14

(2S,3S)-2-Phenyl-3-(quinolin-8-yl)methylpiperidine hydrochloride

The title compound was prepared by a procedure similar to that described in Example 3.

M.p. 252-253°C (dec).

^{1}H NMR (free base, $CDCl_3$) δ 1.38 (m, 1H), 1.58 (m, 1H), 1.94 (m, 1H), 2.17 (m, 1H), 2.78 (m, 2H), 3.24 (m, 1H), 3.83 (d, 1H, J=3), 3.96 (d, 1H, J=15), 4.28 (d, 1H, J=15), 7.14 (m, 6H), 7.32 (m, 2H), 7.58 (t, 1H, J=4), 7.98 (d, 1H, J=6), 8.46 (m, 1H).

HRMS Calc'd for $C_{21}H_{23}N_3$: 317.1887. Found: 317.1883.

Anal. Calc'd for $C_{21}H_{33}N_3 \cdot 3HCl \cdot 1.33\ H_2O$: C, 55.95; H, 6.40; N. 9.32. Found: C, 56.00; H, 6.28; N. 9.16.

EXAMPLE 15

(2S,3S)-3-(5-Heptyloxy-2-methoxybenzyl)amino-2-phenyl-piperidine hydrochloride

The title compound was prepared by a procedure similar to that described in Example 3.

M.p. 230°C (dec).

^{1}H NMR (free base, $CDCl_3$) δ 0.90 (m, 2H), 1.38 (m, 10H), 1.76 (m, 4H), 2.12 (m, 1H), 2.80 (m, 2H), 3.26 (m, 1H), 3.38 (d, 1H, J=15), 3.42 (s, 3H), 3.62 (d, 1H, J=15), 3.82 (t, 2H, J=6), 3.88 (d, 1H, J=3), 6.62 (m, 3H), 7.28 (m, 5H).

HRMS Calc'd for $C_{26}H_{38}N_2O_2$: 410.2928. Found: 410.2953.

EXAMPLE 16

(2S,3S)-3-(2-Heptyloxy-5-methoxybenzyl)amino-2-phenyl-piperidine hydrochloride

The title compound was prepared by a procedure similar to that described in Example 3.

M.p. 212-213°C (dec).

^{1}H NMR (free base, $CDCl_3$) δ 0.90 (m, 3H), 1.60 (m, 13H), 2.12 (m, 1H), 2.80 (m, 2H), 3.26 (m, 1H), 3.36 (d, 1H, J=15), 3.62 (m, 6H), 3.86 (d, 1H, J=3), 6.60 (m, 3H), 7.23 (m, 5H).

HRMS Calc'd for $C_{26}H_{38}N_2O_2$: 410.2928. Found: 410.2912.

Anal. Calc'd for $C_{26}H_{38}N_2O_2 \cdot 2HCl$: C, 64.59; H, 8.34; N, 5.80. Found: C, 64.34; H, 8.20; N, 5.75.

EXAMPLE 17

(2S,3S)-3-(5-Heptyl-2-methoxybenzyl)amino-2-phenylpiperidine hydrochloride

The title compound was prepared by a procedure similar to that described in Example 3.

M.p. 242-243°C (dec).

^1H NMR (free base, $CDCl_3$) δ 0.88 (m, 3H), 1.60 (m, 13H), 2.14 (m, 1H), 2.44 (t, 2H, J=6), 2.78 (m, 2H), 3.26 (m, 1H), 3.40 (m, 4H), 3.64 (d, 1H, J=15), 3.86 (d, 1H, J=2), 6.58 (d, 1H, J=6), 6.75 (d, 1H, J=2), 6.92 (d, 1H, J=6), 7.26 (m, 5H).

HRMS Calc'd for $C_{26}H_{38}N_2O$: 394.2977. Found: 394.3009.

EXAMPLE 18

(2S,3S)-3-(2-Ethylaminobenzyl)amino-2-phenylpiperidine hydrochloride

The title compound was prepared by treatment of the product of Example 10 with borane dimethylsulfide.

M.p. 210-215°C (dec).

^1H NMR (free base, $CDCl_3$) δ 0.97 (t, 3H, J=6), 1.56 (m, 3H), 2.05 (m, 1H), 2.80 (m, 4H), 3.12 (m, 1H), 3.24 (d, 1H, J=12), 3.46 (d, 1H, J=12), 3.82 (d, 1H, J=2), 6.46 (m, 2H), 6.70 (d, 1H, J=6), 7.03 (t, 1H, J=6), 7.22 (m, 5H).

HRMS Calc'd for $C_{20}H_{27}N_3$: 309.2199. Found: 309.2188.

EXAMPLE 19

(2S,3S)-1-(5,6-Difluorohex-1-yl)-3-(2-methoxybenzyl)-amino-2-phenylpiperidine hydrochloride

The title compound was prepared by a procedure similar to that described in Example 2.

M.p. 52-54°C (dec).

^1H NMR (free base, $CDCl_3$) δ 1.44 (m, 7H), 1.88 (m, 2H), 2.00 (m, 3H), 2.51 (m, 2H), 3.18 (m, 1H), 3.26 (d, 1H, J=2), 3.33 (d, 1H, J=15), 3.44 (s, 3H), 3.66 (d, 1H, J=15), 4.40 (m, 3H), 6.60 (d, 1H, J=6), 6.72 (t, 1H, J=6), 6.83 (d, 1H, J=6), 7.07 (t, 1H, J=6), 7.24 (m, 5H).

HRMS Calc'd for $C_{25}H_{34}F_2N_2O$: 416.2639. Found: 416.2653.

Anal. Calc'd for $C_{25}H_{34}F_2N_2O \cdot 2HCl \cdot 1.5H_2O$: C, 58.14; H, 7.61; N, 5.42. Found: C, 58.36; H, 7.81; N, 5.32.

EXAMPLE 20

(2S,3S)-3-(2-Methoxy-5-n-propylbenzyl)amino-2-phenylpiperidine hydrochloride

The title compound was prepared by a procedure similar to that described in Example 3.

M.p. 245-247°C (dec).

^1H NMR (free base, $CDCl_3$) δ 0.9 (m, 3H), 1.4 (m, 1H), 1.54 (m, 2H), 1.92 (m, 1H), 2.14 (m, 1H), 2.44 (t, 2H, J=6), 2.80 (m, 2H), 3.26 (m, 1H), 3.40 (d, 1H, J=15), 3.44 (s, 3H), 3.66 (d, 1H, J=15), 3.90 (s, 1H), 6.56 (d, 1H, J=10), 6.76 (s, 1H), 6.92 (d, 1H, J=10), 7.26 (m, 5H).

HRMS Calc'd for $C_{22}H_{30}N_2O$: 338.2351. Found: 338.2339.

Anal. Calc'd for $C_{22}H_{30}N_2O_2 \cdot 2HCl \cdot 0.25\ H_2O$: C, 63.57; H, 7.81; N, 6.74. Found: C, 63.59; H, 7.66; N, 6.73.

EXAMPLE 21

(2S,3S)-3-(4,5-Dimethyl-2-methoxybenzyl)amino-2-phenylpiperidine hydrochloride

The title compound was prepared by a procedure similar to that described in Example 3.

M.p. 269-270°C (dec).

^1H NMR (free base, $CDCl_3$) δ 1.40 (m, 1H), 1.60 (m, 1H), 1.96 (m, 2H); 2.14 (s, 3H), 2.18 (s, 3H), 2.80 (m, 2H), 3.30 (m, 1H), 3.40 (d, 1H, J=10), 3.42 (s, 3H), 3.62 (d, 1H, J=10), 3.90 (d, 1H, J=3), 6.48 (s, 1H), 6.70 (s, 1H), 7.28 (m, 5H).

HRMS Calc'd for $C_{21}H_{28}N_2O$: 324.2195. Found: 324.2210.

Anal. Calc'd for $C_{21}H_{28}N_2O \cdot 2HCl \cdot 0.25\ H_2O$: C, 62.80; H, 7.60; N, 6.99. Found: C, 62.64; H, 7.31; N, 6.86.

EXAMPLE 22

(2S,3S)-3-(5-t-Butyl-2-hydroxybenzyl)amino-2-phenylpiperidine hydrochloride

The title compound was prepared by a procedure similar to that described in Example 3.

M.p. >130°C (dec).

^{1}H NMR (free base, $CDCl_3$) δ 1.2 (s, 9H), 1.6 (m, 3H), 2.1 (m, 1H), 2.72 (m, 1H), 2.90 (s, 1H), 3.16 (m, 1H), 3.38 (d, 1H, J=15), 3.50 (d, 1H, J=15), 3.90 (d, 1H, J=3), 6.62 (d, 1H, J=10), 6.68 (d, 1H, J=3), 7.08 (d, 1H, J=10), 7.32 (m, 5H).

HRMS Calc'd for $C_{22}H_{30}N_2O$: 338.2351. Found: 338.2384.

EXAMPLE 23

(2S,3S)-3-(5-Carbomethoxy-2-methoxybenzyl)amino-2-phenylpiperidine hydrochloride

The title compound was prepared by a procedure similar to that described in Example 3.

M.p. 238-240°C (dec).

^{1}H NMR (free base, $CDCl_3$) δ 1.4 (m, 1H), 1.6 (m, 1H), 1.88 (m, 2H), 2.1 (m, 1H), 2.75 (m, 2H), 3.2 (m, 1H), 3.35 (d, 1H, J=15), 3.45 (s, 3H), 3.7 (d, 1H, J=15), 3.85 (m, 4H), 6.65 (d, 1H, J=10), 7.2 (m, 5H), 7.70 (d, 1H, J=3), 7.85 (m, 1H).

HRMS Calc'd for $C_{21}H_{26}N_2O_3$: 354.1937. Found: 354.1932.

EXAMPLE 24

(2S,3S)-3-(5-n-Butyl-2-methoxybenzyl)amino-2-phenylpiperidine hydrochloride

The title compound was prepared by a procedure similar to that described in Example 3.

M.p. 252-253°C (dec).

^{1}H NMR (free base, $CDCl_3$) δ 0.96 (m, 3H), 1.38 (m, 3H), 1.56 (m, 3H), 1.96 (m, 2H), 2.18 (m, 1H), 2.50 (m, 2H), 2.86 (m, 2H), 3.30 (m, 1H), 3.44 (d, 1H, J=15), 3.48 (s, 3H), 3.68 (d, 1H, J=15), 3.92 (d, 1H, J=3), 6.62 (d, 1H, J=10), 6.80 (s, 1H), 6.96 (d, 1H, J=10), 7.30 (m, 5H).

Anal. Calc'd for $C_{23}H_{32}N_2O \cdot 2HCl \cdot 0.33\ H_2O$: C, 64.03; H, 8.09; N, 6.50. Found: C, 64.39; H, 7.90; N, 6.59.

EXAMPLE 25

(2S,3S)-3-(5-Isopropyl-2-methoxybenzyl)amino-2-phenylpiperidine hydrochloride

The title compound was prepared by a procedure similar to that described in Example 3.

M.p. 252-254°C.

^{1}H NMR (free base, $CDCl_3$) δ 1.14 (d, 6H, J=6), 1.24 (m, 1H), 1.58 (m, 1H), 1.78 (m, 1H), 2.1 (m, 1H), 2.76 (m, 3H), 3.24 (m, 1H), 3.36 (d, 1H, J=12), 3.42 (s, 3H), 3.60 (d, 1H, J=12), 3.86 (d, 1H, J=3), 6.56 (d, 1H, J=6), 6.80 (d, 1H, J=3), 6.84 (m, 1H), 7.24 (m, 5H).

HRMS Calc'd for $C_{22}H_{30}N_2O$: 338.2351. Found: 338.2377.

Anal. Calc'd for $C_{22}H_{30}N_2O \cdot 2HCl \cdot 0.26\ H_2O$: C, 63.52; H, 7.88; N, 6.74. Found: C, 63.33; H, 7.64, N, 6.75.

EXAMPLE 26

(2S,3S)-1-(4-t-Butyramidobut-1-yl)-3-(2-methoxybenzyl)-amino-2-phenylpiperidine hydrochloride

The title compound was prepared by a procedure similar to that described in Example 4.

^{1}H NMR (free base, $CDCl_3$) δ 1.1 (s, 9H), 1.4 (m, 2H), 1.64 (m, 6H), 1.98 (m, 2H), 2.48 (m, 2H), 3.08 (m, 2H), 3.24 (d, 1H, J=3), 3.32 (d, 1H, J=15), 3.38 (s, 3H), 3.42 (d, 1H, J=15), 3.64 (d, 1H, J=15), 6.58 (d, 1H, J=10), 6.70 (m, 1H), 6.80 (d, 1H, J=10), 7.08 (m, 1H), 7.26 (s, 5H).

HRMS Calc'd for $C_{28}H_{41}N_3O_2$: 451.3189. Found: 451.3123.

EXAMPLE 27

(2S,3S)-(3-Benzamidoprop-1-yl)-3-(2-methoxybenzyl)-amino-2-phenylpiperidine hydrochloride

The title compound was prepared by a procedure similar to that described in Example 4.

M.p. 98°C (dec).

^{1}H NMR (free base, $CDCl_3$) δ 1.4 (m, 3H), 1.96 (m, 6H), 2.58 (m, 1H), 2.67 (m, 1H), 3.1 (m, 1H), 3.22 (d, 1H, J=3), 3.32 (s, 3H), 3.42 (d, 1H, J=15), 3.74 (d, 1H, J=15), 3.94 (m, 1H), 6.59 (d, 1H, J=10), 6.70 (m, 1H), 6.82 (d, 1H, J=10), 7.06 (m, 1H), 7.30 (m, 8H), 8.06 (d, 2H, J=10), 8.52 (m, 1H).

HRMS Calc'd for $C_{29}H_{34}N_3O_2$: 456.2643. Found: 456.2613.

EXAMPLE 28

cis-3-(5-Cyclopentyl-2-methoxybenzyl)amino-2-phenyl-piperidine hydrochloride

The title compound was prepared by a procedure similar to that described in Example 1.

M.p. 244-246°C.

^{1}H NMR (free base, $CDCl_3$) δ 1.40-2.10 (m, 12H), 2.17 (d, 1H), 2.7-2.95 (m, 3H), 3.3 (d, 1H), 3.45 (d, 1H, J=13), 3.50 (s, 3H), 3.68 (d, 1H, J=13), 3.90 (d, 1H, J=2), 6.66 (d, 1H, J=7), 6.85 (d, 1H, J=2), 7.0 (dd, 1H), 7.20-7.40 (m, 6H).

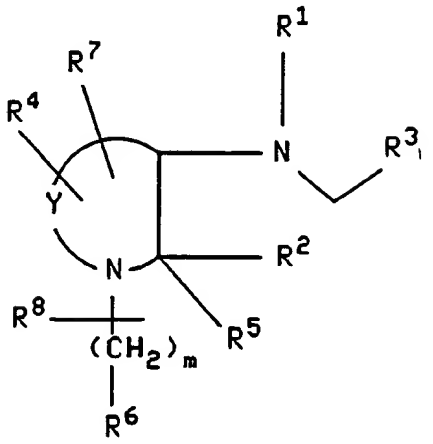
^{13}C NMR (free base, $CDCl_3$) δ 20.3, 25.4, 28.2, 34.7, 34.8, 45.1, 46.8, 47.8, 54.9, 64.0, 109.6, 125.9, 126.4, 126.5, 126.6, 127.8, 128.1, 128.2, 128.4, 137.8, 142.4, 155.7.

Mass spectrum: m/z 364 (parent).

Anal. Calc'd for $C_{24}H_{32}N_2O \cdot 2HCl \cdot 0.5\ H_2O$: C, 64.57; H, 7.90; N, 6.27. Found: C, 64.75; H, 7.66; N, 6.40.

CLAIMS

1. A compound of the formula



I

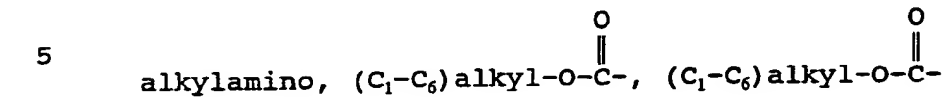
wherein Y is $(CH_2)_n$ wherein n is an integer from 1 to 6, and wherein any one of the carbon-carbon single bonds in said $(CH_2)_n$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_n$ may optionally be substituted with R^4, and wherein any one of the carbon atoms of said $(CH_2)_n$ may optionally be substituted with R^7;

m is an integer from 0 to 8, and any one of the carbon-carbon single bonds of said $(CH_2)_m$ may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^8;

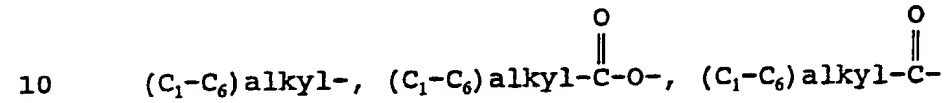
R^1 is hydrogen or (C_1-C_8) alkyl optionally substituted with hydroxy, alkoxy or fluoro;

R^2 is a radical selected from hydrogen, (C_1-C_6) straight of branched alkyl, (C_3-C_7) cycloalkyl wherein one of the carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl (C_2-C_6) alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl (C_2-C_6) alkyl and benzhydryl may optionally

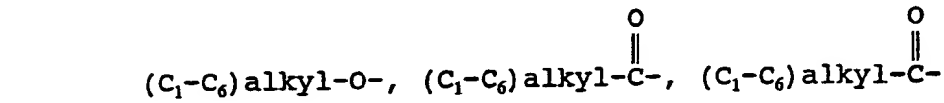
be substituted with one or more substituents independently selected from halo, nitro, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, amino, (C_1-C_6)-



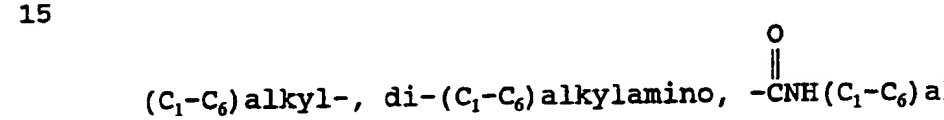
alkylamino, (C_1-C_6)alkyl-O-C-, (C_1-C_6)alkyl-O-C-



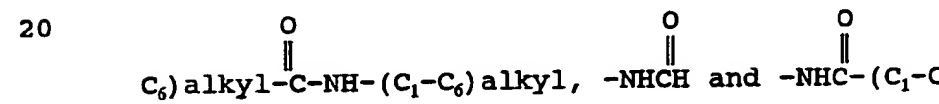
(C_1-C_6)alkyl-, (C_1-C_6)alkyl-C-O-, (C_1-C_6)alkyl-C-



(C_1-C_6)alkyl-O-, (C_1-C_6)alkyl-C-, (C_1-C_6)alkyl-C-



(C_1-C_6)alkyl-, di-(C_1-C_6)alkylamino, -CNH(C_1-C_6)alkyl, (C_1-



C_6)alkyl-C-NH-(C_1-C_6)alkyl, -NHCH and -NHC-(C_1-C_6)alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

R^5 is hydrogen, phenyl or (C_1-C_6)alkyl;

or R^2 and R^5, together with the carbon to which they are attached, form a saturated carbocyclic ring having from 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by oxygen, nitrogen or sulfur;

R^3 is aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; and cycloalkyl having 3 to 7 carbon atoms wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said (C_3-C_7) cycloalkyl may optionally be substituted with one or two substituents, each of said substituents being independently selected from halo, nitro, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, methyl, trifluoromethyl, phenyl,

amino, (C_1-C_6) alkylamino, $-CNH(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-C-$, $NH-(C_1-C_6)alkyl$, $-NHCH$ and $-NHC-(C_1-C_6)alkyl$; and

R^4 and R^7 are each independently selected from hydrogen, hydroxy, halo, amino, oxo (=O), nitrile, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, (C_1-C_6)alkoxy, $(C_1-C_6)alkyl-O-C-$, $(C_1-C_6)alkyl-O-C-(C_1-C_6)alkyl-$, hydroxy-$(C_1-C_6)$alkyl, (C_1-C_6)alkoxy-(C_1-C_6)alkyl, $(C_1-C_6)alkyl-C-O-$, $(C_1-C_6)alkyl-C-(C_1-C_6)alkyl-O-$, $(C_1-C_6)alkyl-C-$, $(C_1-C_6)alkyl-C-(C_1-C_6)alkyl-$, and the radicals set forth in the definition of R^2;

R^6 is $NHCR^9$, $NHCH_2R^9$, SO_2R^9 or one of the radicals set forth in any of the definitions of R^2, R^4 and R^7;

R^8 is oximino (=NOH) or one of the radicals set forth in any of the definitions of R^2, R^4 and R^7;

R^9 is (C_1-C_6)alkyl, hydrogen, phenyl, or phenyl (C_1-C_6)alkyl;

with the proviso that (a) when m is 0, R^8 is absent, (b) neither R^4, R^6, R^7, nor R^8 can form, together with the carbon to which it is attached, a ring with R^5, (c) when R^4 and R^7 are attached to the same carbon atom, then either each of R^4 and R^7 is independently selected from hydrogen, fluoro and (C_1-C_6) alkyl, or R^4 and R^7, together with the carbon to which they are attached, form a (C_3-C_6) saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are attached, (d) when n is 2 and either R^4 or R^7 is 5-hydroxy(C_1-C_6)alkyl or 5-(C_1-C_6)alkoxy-(C_1-C_6)alkyl, then the other of R^4 and R^7 is

hydrogen, and (e) when n is 2, neither R^4 nor R^7 is 4-hydroxy(C_1-C_6)alkyl or 4-(C_1-C_6)alkoxy-(C_1-C_6)alkyl; and (f) in all compounds of the formula I, either R^3 is aryl substituted with at least one phenyl group, or one or both of R^4 and R^7 is hydroxy-(C_1-C_6)alkyl or (C_1-C_6)alkoxy-(C_1-C_6)alkyl.

and the pharmaceutically acceptable acid addition salts thereof.

2. A compound selected from the group consisting of:

(2S,3S)-3-(4,5-difluoro-2-methoxybenzyl)amino-2-phenyl-piperidine;

(2S,3S)-3-(2-cyclopentyloxy-5-methoxybenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(5-sec-butyl-2-methoxybenzyl)amino-2-phenyl-piperidine;

(2S,3S)-3-(5-tert-butyl-2-methoxybenzyl)amino-2-phenyl-piperidine;

(2S,3S)-3-(2-cyclopentyloxybenzyl)amino-2-phenyl-piperidine;

(2S,3S)-3-(2-acetamidobenzyl)amino-2-phenylpiperidine;

(2S,3S)-3-(5-ethyl-2-methoxybenzyl)amino-2-phenyl-piperidine hydrochloride;

(2S,3S)-3-(4-amino-5-chloro-2-methoxybenzyl)amino-2-phenylpiperidine hydrochloride;

(2S,3S)-2-phenyl-3-(quinolin-8-yl)methylpiperidine hydrochloride;

(2S,3S)-3-(5-heptyloxy-2-methoxybenzyl)amino-2-phenyl-piperidine hydrochloride;

(2S,3S)-3-(2-heptyloxy-5-methoxybenzyl)amino-2-phenyl-piperidine hydrochloride;

(2S,3S)-3-(5-heptyl-2-methoxybenzyl)amino-2-phenyl-piperidine hydrochloride;

(2S,3S)-3-(2-ethylaminobenzyl)amino-2-phenylpiperidine hydrochloride;

(2S,3S)-1-(5,6-difluorohex-1-yl)-3-(2-methoxybenzyl)-amino-2-phenylpiperidine hydrochloride;

(2S,3S)-3-(2-methoxy-5-n-propylbenzyl)amino-2-phenyl-piperidine hydrochloride;

(2S,3S)-3-(4,5-dimethyl-2-methoxybenzyl)amino-2-phenyl-piperidine hydrochloride;

(2S,3S)-3-(5-t-butyl-2-hydroxybenzyl)amino-2-phenyl-piperidine hydrochloride;

(2S,3S)-3-(5-carbomethoxy-2-methoxybenzyl)amino-2-phenylpiperidine hydrochloride;

(2S,3S)-3-(5-n-butyl-2-methoxybenzyl)amino-2-phenyl-piperidine hydrochloride;

(2S,3S)-3-(5-isopropyl-2-methoxybenzyl)amino-2-phenyl-piperidine hydrochloride;

(2S,3S)-1-(4-t-butyramidobut-1-yl)-3-(2-methoxybenzyl)-amino-2-phenylpiperidine hydrochloride;

(2S,3S)-(3-benzamidoprop-1-yl)-3-(2-methoxybenzyl)-amino-2-phenylpiperidine hydrochloride; and

cis-3-(5-cyclopentyl-2-methoxybenzyl)amino-2-phenyl-piperidine hydrochloride.

3. A pharmaceutical composition for treating or preventing a condition selected from the group consisting of inflammatory diseases, anxiety, colitis, depression or dysthymic disorders, psychosis, pain, allergies, chronic obstructive airways disease, hypertension, hypersensitivity disorders, vasospastic diseases, fibrosing and collagen diseases, reflex sympathetic dystrophy, addiction disorders, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders, disorders related to immune enhancement or suppression and rheumatic diseases in a mammal, comprising an amount of a compound according to claim 1 or claim 2 effective in preventing or treating such condition and a pharmaceutically acceptable carrier.

4. A method of treating or preventing a condition selected from the group consisting of inflammatory diseases anxiety, colitis, depression or dysthymic disorders, psychosis, pain, allergies, chronic obstructive airways disease, hypertension, hypersensitivity disorders,

vasospastic diseases, fibrosing and collagen diseases, reflex sympathetic dystrophy, addiction disorders, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders, disorders related to immune enhancement or suppression and rheumatic diseases in a mammal, comprising administering to a mammal in need of such treatment or prevention an amount of a compound according to claim 1 or claim 2 effective in preventing or treating such condition.

5. A pharmaceutical composition for treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound according to claim 1 or claim 2 effective in antagonizing the effect of substance P at its receptor site and a pharmaceutically acceptable carrier.

6. A method of treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising administering to a mammal in need of such treatment or prevention an amount of a compound according to claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site.

7. A pharmaceutical composition for treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound according to claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such condition and a pharmaceutically acceptable carrier.

8. A method of treating or preventing a condition in mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated

neurotransmission, comprising administering to a mammal in need of such treatment or prevention an amount of a compound according to claim 1 or claim 2 effective in treating or preventing such condition.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/04008

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D211/56; A61K31/395; C07D211/14; C07D215/02
C07D409/12; C07D407/12; C07D401/12; C07D417/12

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
P,X	EP,A,0 436 334 (PFIZER) 10 July 1991 see the whole document	1-8
A	DE,A,2 600 557 (DELMAR CHEMICALS) 14 July 1977 see the whole document	1-8

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
14 OCTOBER 1992	23.11.92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	GETTINS M.P.

INTERNATIONAL SEARCH REPORT

Inte tional application No.

PCT/US92/04008

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Given the extremely large number of compounds resulting from the combination of the symbols defined in formula I (especially Y) and in the light of the examples the search has been limited to compounds of formula (I) which are piperidine derivatives.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9204008 SA 60465

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 14/10/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0436334	10-07-91	WO-A- 9109844	11-07-91
DE-A-2600557	14-07-77	None	

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82